RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-62 were pending as of the Response to Office Action dated October 3, 2003. Claims 33-37 had been withdrawn by the examiner. In the Office Action Dated June 3, 2004, claims 1-32 and 38-62 were rejected.

Herein, claim 32 is cancelled and claim 48 is amended. Thus, claims 1-31 and 38-62 are the subject of this response.

B. Amendment to Specification

Applicants appreciate the Examiner pointing out the typographical error in the previous attempted amendment to the priority claim. Applicants have submitted a new amendment herewith that disclaims priority but retains the incorporation by reference of the two earlier applications.

C. Claims 32 and 48 Are Not Indefinite

The Action rejects claims 32 and 48 under 35 U.S.C. §112, second paragraph, as being indefinite. To address the Action's concerns, claim 32 has been cancelled as essentially duplicative of claim 31, and claim 48 has been amended as suggested by the Examiner.

D. Provisional Double Patenting Rejection

The Action provisionally rejects claims 1, 3-29, 38, 47-62 under the judicially created doctrine of obviousness-type double patenting over claims 1-29 of U.S. Publication No. 2002/018723 (U.S. Application Ser. No. 09/880,609).

In response, Applicants note that the claims now pending in the '609 prosecution are believed to be patentably distinct from the present case. For the Examiner's convenience,

Applicants enclose herewith a copy of those claims (Exhibit 1). In any event, because this rejection is provisional, Applicants will address the rejection once claims in either application are deemed in condition for allowance.

E. Claims Are Novel

1. Claims 3, 8, 9, 13-25, 31, 32, 38, 47, 49, and 51-62 Are Not Anticipated by Huyghe *et al.* in Light of Kuchler

The Action rejects claims 1, 3, 8, 9, 13-25, 31, 32, 38, 47, 49, and 51-62 under 35 U.S.C. §102(b) as being anticipated by Huyghe *et al.* ("Huyghe") in light of Kuchler. More specifically, it alleges that Huyghe teaches the preparation of adenovirus by preparing a culture of 293 producer cells that have attained an essentially homogenous confluency of 50-60% when the cells are infected with a replication-defective adenovirus. The Action asserts that this percentage of confluency reasonably corresponds to mid-log phase of cell growth based on information on the 293 cells regarding lag time, confluency, time of attachment to the surface of the plate, and on the chart provided by Kuchler. Applicants respectfully traverse this rejection.

First, for the record it is noted that the Examiner's characterization of the present claims in the paragraph on page 5 that begins "[t]he claims are drawn ..." is apparently a recitation of various narrower claims and is not intended to be a recitation of what the Examiner contends the broadest claims cover.

The Examiner's principal position as to why Huyghe is now being reasserted as anticipatory is apparently based on the following:

1. The Examiner reasons, at the bottom of page 6, that "seeding density is established in the art as a crucial component of the log phase" and thus, since Huyghe *et al.* is silent as to the seeding density, "applicant's presumption of early log phase density for the cells" is "speculative and unsubstantiated."

Applicants respond to this argument by incorporating by reference the arguments set forth in detail in the Amendment dated February 13, 2002, including the declaration of Shawn Gallagher. Further, it is noted that Mr. Gallagher provided what he understood to be a reasonable assumption regarding seeding density, there being no such information given in Huyghe *et al.* Applicants also stand behind the numerous additional bases relied upon in the declaration. Finally, since it is the Examiner's position that due to the absence of information regarding seeding density any conclusions drawn from Huyghe are "speculative and unsubstantiated" then it can only be concluded that the Examiner has failed to make a *prima facie* case of anticipation, since the Examiner's position is also "speculative and unsubstantiated." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (stating that anticipation "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.").

2. With regard to Mediatech's Technical Information, the Examiner states that Mr. Gallagher's conclusion that 50-60% confluency equates to early log phase is unsupported in that Mediatech simply states that 70% confluent cultures are in log phase and "there is no differentiation between the various stages of log growth and % confluency provided by" the reference.

The Examiner mischaracterizes Mr. Gallagher's testimony and also mischaracterizes the reference. Mediatech does not simply state that 70% confluent cultures are in log phase. Rather, it stands for the proposition that one should use 70% confluent cultures to ensure that they are in log phase. This implies, as testified to by Mr. Gallagher, that cultures that are less confluent that 70% can not be assured of even being in log phase. The Examiner has provided no contravening evidence.

3. Lastly, referring to Kuchler, the Examiner states that the chart provided by Kuchler (presumably Figure 3-1) indicates that "the growth curve of cells after 60 hours of incubation is the mid-point of the growth curve, *i.e.*, mid-phase" and that

Huyghe *et al.* teaches to infect at between 2 and 2.5 days (*i.e.*, between 48 and 60 hours)

In response to the argument, the Applicants first note that the Kuchler reference was merely relied upon by Mr. Gallagher for its general statement that a typical lag phase is between 24 and 48 hours. See Gallagher declaration, paragraph 10. The Examiner now refers to Figure 1-3 of Kuchler, which concerns the growth of L-M mouse fibroblasts grown in suspension culture, and attempts to argue that this figure somehow stands for the general proposition that at 60 hours (*i.e.*, at 2.5 days) of culture plate growth, the Huyghe 293 cells would have just arrived at mid-log growth. The Examiner's reasoning is erroneous for several reasons.

First and foremost, there is no explanation of why or how the Kuchler reference, which discusses L-M fibroblast cells in suspension, relates to what Huyghe purportedly teaches. The Examiner has not identified any connection between L-M fibroblast cells in suspension and 293 cells grown on plates.

Second, even if Kuchler were relevant to what Huyghe teaches, it appears that in the chart relied upon by the Examiner that the growth curve shows the cells to be slightly *before* mid-log phase at 60 hours. This chart does not provide evidence that the cells of Huyghe were infected after mid-log phase of growth.

Finally, it appears as though the L-M cells grown in suspension culture had a doubling time of somewhat less than 24 hours (approx. 2.5×10^5 cells at 24 hours; approx. 5.6×10^5 cells at 48 hours; approx. 8.5×10^5 at 60 hours; approx. 1.8×10^6 at 84 hours; which works out to about a 16 to 20 hrs doubling time) A 16-20 hour doubling time would mean that the L-M cells would be expected to arrive at mid-log much quicker than a cell having a doubling time of 36 hours as assumed by Mr. Gallagher for his 293 cell calculations. Mr. Gallagher earlier stated only that the cells were probably at latest in early-log phase and Kuchler was cited merely to

indicate merely that the lag phase, which precedes the log phase, is said to vary from 24 to 48 hours.

The doubling time for 293 is consistent with that measured at the assignee of the present application, Introgen Therapeutics, Inc. (See enclosed Declaration of Dr. Zhang (Exhibit 2), showing a doubling time of approx. 30 hours for 293 cells in T-150 flasks.) Assuming a doubling time of 30 hours as compared to the 16-20 hour doubling time shown in Kuchler's Figure 1-3, the growth curve of Figure 1-3 would be well below mid-log.

In light of the foregoing, it is Applicants' position that taking into account all of the evidence, the Examiner has failed to make a *prima facie* case that the 293 cells of Huyghe were infected at or after mid-log phase. Indeed, the evidence strongly supports the conclusion that the cells were, at best, in early log phase.

Accordingly, Applicants respectfully request this rejection be withdrawn.

2. Claims 1, 3, 8, 9, 13-25, 31, 32, 38, 47, 49, and 51-62 Are Not Anticipated by Zhang *et al.* as Further Evidenced by Wu *et al.*

The Action rejects claims 1, 3, 8, 9, 13-25, 31, 32, 38, 47, 49, and 51-62 under 35 U.S.C. §102(a) as being anticipated by Zhang *et al.* (WO 98/22588) ("Zhang PCT"), as further evidenced by Wu *et al.* (U.S. Patent 6,689,600) ("Wu"). It also rejects these claims under 35 U.S.C. § 102(e) as being anticipated by the U.S. patent counterpart of Zhang *et al.* (U.S. Patent 6,194,191) ("Zhang Patent") (collectively "Zhang references"). The Action contends that while the Zhang references do not specifically teach infecting with adenovirus at the "mid-log" phase, the cells are determined to be at least mid-phase based on the 80% to 90% confluence and the types of conditions the cells are cultured in. It asserts that Wu teaches that the Zhang references disclose cells that are infected after mid-phase. Applicants respectfully traverse this rejection.

In response, Applicants have enclosed the Declaration of Dr. Shuyuan Zhang to demonstrate that the invention disclosed but not claimed in the Zhang references was derived from the inventors of the subject claims. *See* Exhibit 2. The Action states that the Zhang references anticipate "a process of preparing adenovirus by preparing a culture of producer cells essentially homogenous with respect to growth, infecting the producer cells with adenovirus between mid-log and stationary phase, and harvesting the adenovirus and placing the virus into a pharmaceutically acceptable composition." Action at page 9. Dr. Zhang indicates in his declaration that this process was invented by him and the other co-inventors who are listed as inventors on both the present application and the Zhang references.

Because neither of the Zhang references is proper prior art with respect to independent claims 1 and 47, claims 1 and 47 are not anticipated by the Zhang references under 102(a) or 102(e). Moreover, as the remaining rejected claims are ultimately dependent from either independent claim 1 or claim 47, none of these claims can be anticipated by these references as well.

Additionally, reliance on the Wu reference is inappropriate. Wu is simply not prior art. Furthermore, to the extent that it comments about the teachings of the Zhang references, the statements do not evidence what one of ordinary skill in the art understood from the Zhang reference because the inventors on the Wu reference are inventors of the Zhang reference.

The Zhang references are not prior art and they do not anticipate the claimed invention. Accordingly, Applicants respectfully request this rejection be withdrawn.

F. Claims Are Not Obvious

1. Claims 10-12 and 29 Are Not Rendered Obvious by Huyghe

The Action rejects claims 10-12 and 29 under 35 U.S.C. §103(a) as being unpatentable over Huyghe as applied to claims 1, 3, 8, 9, 13-25, 31, 32, 38, 47, 49, and 51-62. It contends that although Huyghe does not teach specific cell numbers to be plated (claims 10-12), those numbers would be a subjective determination by one of ordinary skill in the art based on many factors, such as type of cell, the condition of the cells before plating, and the nature of the cell's division, etc. It concludes that it would be *prima facie* obvious for one skilled in the art to determine the appropriate number of cells to plate for each situation encountered. The Action also alleges that although Huyghe does not teach a harvested adenovirus with the characteristics listed in claim 29, this claim is obvious because it would have been obvious to one of ordinary skill in the art to test any for any of these properties to ensure a good yield of adenovirus. Applicants respectfully traverse this rejection.

With respect to the rejection of claims 10-12, Applicants note that the Examiner has, in the rejection over Huyghe observed that "seeding density is established in the art as a crucial component of the log phase." This argument would appear to be inconsistent with the Examiner's position now that seeding density is merely a subjective determination. In any event, the rejection as to Huyghe cannot stand for the reasons discussed in section E above, because these claims all depend ultimately from claim 1.

With respect to the rejection of claim 29 over Huyghe *et al.*, Applicants observe that claim 29 sets forth specific purity limitations and the Examiner has not explained how Huyghe *et al.* teaches or suggests adenovirus preparations meeting these limitations. Moreover, Huyghe *et al.* is not relevant to the subject matter of claim 29, for the reasons discussed in section E above, since these claims all depend ultimately from claim 1.

2. Claims 10-12 and 29 Are Not Rendered Obvious by Either Zhang Reference

The Action rejects claims 10-12 and 29 under 35 U.S.C. §103(a) as being unpatentable over either Zhang reference as applied to claims 1, 3-9, 13-28, 30-32, 38-49, and 51-62. It contends that although neither Zhang reference teaches specific cell numbers to be plated (claims 10-12), those numbers would be a subjective determination by one of ordinary skill in the art based on many factors, such as type of cell, the condition of the cells before plating, and the nature of the cell's division, etc. It concludes that it would be *prima facie* obvious for one skilled in the art to determine the appropriate number of cells to plate for each situation encountered. The Action also alleges that although the Zhang references do not teach a harvested adenovirus with the characteristics listed in claim 29, this claim is obvious because it would have been obvious to one of ordinary skill in the art to test any for any of these properties to ensure a good yield of adenovirus. Applicants respectfully traverse this rejection.

Applicants refer the Examiner to the enclosed declaration of Dr. Zhang. As discussed above, the Zhang references are not proper prior art with respect to the independent claims. Accordingly, Applicants respectfully request this rejection be withdrawn.

3. Claims 2 and 50 Are Not Rendered Obvious by Huyghe in View of Graham *et al.* and Leu *et al.*

The Action rejects claims 2 and 50 under 35 U.S.C. §103(a) as being unpatentable over Huyghe as applied to claims 1, 3, 8, 9-25, 29, 31, 32, 38, 47, 49, and 51-62, further in view of Graham *et al.* (C31 on IDS) ("Graham") and Leu *et al.* ("Leu"). More specifically, it contends that although Huyghe does not teach infecting cells at late-log to stationary phase of cell-growth, Leu teaches infecting cells at late-log. The Action argues that one would have been motivated to

propagate the adenovirus of Huyghe with the cell culture method steps of infection of Leu to increase the amount of adenovirus produced in cell culture. It also alleges that one of ordinary skill in the art would have had a reasonable expectation of success because Leu teaches that a wide range of viruses may be propagated to generate vaccines using the method steps. The Graham reference is used by the examiner to support the argument that cells can be infected at 80% to 90% confluency, which she argues demonstrates that the teachings of Leu are applicable to adenovirus infection at late-log phase of growth. It concludes that the invention would have been *prima facie* obvious for one skilled in the art absent unexpected results. Applicants respectfully traverse this rejection.

In response, Applicants incorporate by reference the positions set forth in the previous response and supported by the previously submitted Zhang declaration. The Examiner presents no cognizable arguments in response—merely stating that Leu is "applicable to the general viral propagation art" does not make it so, and does not make its teachings relevant to adenoviruses. Dr Zhang provides substantial reasoning as to why one of skill in the art would not look to Leu. to solve problems with respect to adenovirus culturing. Also, the excerpt in Leu that concerns the viruses other than hepatitis merely refers to viruses that can be propagated in the particular hosts, and in no way teaches or suggests that one should employ late-log-phase infection of ***these*** viruses, much less adenoviruses. Lastly, and most importantly, the Examiner has failed to adequately explain how Leu can be combined with Huyghe—throughout the entire Leu reference there is no indication regarding any benefit of employing the particular timing of infecting the cell culture at the time that is recited in the claims—that is, late log or early stationary phase of growth. The reference does not say that this timing leads, for example, to increased hepatitis A virus production.

Further, Leu do not address whether using the mid-log phase of growth, late log phase of growth, or stationary phase of growth to infect a cell culture would in any way be beneficial in achieving increased production of any other virus, including adenovirus. Similarly, there is no teaching or suggestion from Huyghe that there is a problem that needs to be solved. Consequently, neither reference recognizes a problem and thus there is no reason why a skilled artisan would turn to this particular aspect of the virus production process described in Leu reference. A "patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified." *In re Sponnoble*, 160 U.S.P.Q. 237, 243 (C.C.P.A. 1969). A corollary to these principles is where the prior art fails to recognize the existence of a problem in the first place. In this regard, the CCPA has held that it is improper to conclude that an invention is obvious absent evidence that one of skill would have recognized that an underlying problem existed. *In re Nomiya*, 184 U.S.P.Q. 607 (CCPA 1975).

As noted in passing above, the caselaw strongly supports a conclusion of non-obviousness in the present case. The Supreme Court, in *Eibel Process*, noted that the discovery of the source of a known problem is strong evidence of non-obviousness:

> ... we must not lose sight of the fact that one essential part of Eibel's discovery was that the trouble causing the defective paper product under high machine speed was in the disturbance and ripples some ten feet from the discharge and that they were due to the unequal speeds of stock and wire at that point and could be remedied by equalizing the speeds. The invention was not the mere use of a high or substantial pitch to remedy a known source of trouble. ***It was the discovery of the source not before known and the application of the remedy for which Eibel was entitled to be rewarded in his patent.***

Eibel, 261 U.S. at 67-68. (emphasis supplied). *See also Sponnoble*, 160 U.S.P.Q. at 243 ("It should not be necessary for this court to point out that a patentable invention may lie in the

discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.").

Perhaps most relevant to our situation is the *Nomiya* case, where the CCPA, relying on the principles of *Eibel Process* and *Sponnoble*, held that invention is found in the recognition of a previously unknown problem:

> If, as appellants claim, there is no evidence of record that a person of ordinary skill in the art at the time of appellants' invention would have expected the problem in the IGFET to exist at all, ***it is not proper to conclude that the invention which solves this problem, which is claimed as an improvement of the prior art device, would have been obvious to that hypothetical person of ordinary skill in the art.*** This significance of evidence that a problem was know in the prior art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution. Logically, the instant situation is one step removed from the circumstances illustrated by [Eibel Process], where the rippling in paper produced on Fourdrinier paper-making machines was known, but the source of the problem was not.

Nomiya, 184 U.S.P.Q. at 612-13. (emphasis supplied)

In the present case, as in *Nomiya*, the Action fails to present substantial evidence that those of skill recognized the existence or source of the problem with the large-scale production of adenovirus.

"[I]t is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986). The Action does not supply a reason for turning to the Leu reference only for its timing of infection, and therefore, the basis for this rejection is impermissible. It appears that the Examiner is seeking to employ hindsight reconstruction to pick and choose among isolated disclosures in the prior art to render the instant invention as obvious. *See In re Fritch*, 972 F.2d 1260, 23

U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Federal Circuit has repeatedly held that such hindsight reconstruction is an improper basis for a §103 rejection. *See id.*

Thus, given the reasons discussed above and provided in the earlier declaration of Dr. Shuyuan Zhang, one of ordinary skill in the art would not be motivated to combine the teachings of Leu with the teachings of Huyghe (or Zhang *et al.*, discussed below) to prepare an adenovirus of the instant invention. Accordingly, the rejection based on the combination of Leu with that of Huyghe does not meet a necessary criteria required to establish a *prima facie* case of obviousness. Consequently, Applicants respectfully request this rejection be withdrawn.

4. Claims 2 and 50 Are Not Rendered Obvious by Either Zhang Reference in View of Graham and Leu

The Action rejects claims 2 and 50 under 35 U.S.C. §103(a) as being unpatentable over either Zhang reference as applied to claims 1, 3-32, 38-49, and 51-62, and further in view of Graham and Leu. More specifically, it contends that although neither Zhang reference teaches infecting cells at late-log to stationary phase of cell-growth, Leu teaches infecting cells at late-log. The Action argues that one would have been motivated to propagate the adenovirus of Zhang with the cell culture method steps of infection of Leu to increase the amount of adenovirus produced in cell culture. It also alleges that one of ordinary skill in the art would have had a reasonable expectation of success because Leu teaches that a wide range of viruses may be propagated to generate vaccines using the method steps. The Graham reference is used by the examiner to support the argument that cells can be infected at 80% to 90% confluency, which she argues demonstrates that the teachings of Leu are applicable to adenovirus infection at late-log phase of growth. It concludes that the invention would have been *prima facie* obvious for one skilled in the art absent unexpected results. Applicants respectfully traverse this rejection.

Given the reasons discussed above and provided in the earlier declaration of Dr. Shuyuan Zhang, one of ordinary skill in the art would not be motivated to combine the teachings of Leu with the teachings of either Zhang reference as well to prepare an adenovirus of the instant invention. Accordingly, the rejection based on the combination of Leu with that of Zhang *et al.* does not meet a necessary criteria required to establish a *prima facie* case of obviousness. Consequently, Applicants respectfully request this rejection be withdrawn.

5. Claims 26-28 Are Not Rendered Obvious by Graham

The Action rejects claims 26-28 under 35 U.S.C. §103(a) as being unpatentable over Graham. Graham is said to teach that 5% SDS can be used to disrupt cells. The Action contends it would have been obvious to use a detergent as another way of lysing cells. Applicants respectfully traverse this rejection.

Claims 26-28 depend from claim 1, which, as stated *supra*, is not made obvious by Leu, Huyghe., and either Zhang reference, as this combination does not teach the claimed invention. The addition of the teachings of Graham does not cure the deficiencies of Leu, Huyghe, and either Zhang reference. The Graham reference is cited only for its teaching of 5% deoxycholate, which does not provide any motivation to combine the references of Leu, Huyghe, and a Zhang reference. Therefore, claims 26-28 are not make obvious by the combinations of these four references.

In light of all the foregoing, Applicants respectfully request that the Examiner reconsider this issue and withdraw the rejection as to claims 26-28.

6. Claims 4, 30, 39-46, and 48 Are Not Rendered Obvious by Huyghe, Further in View of Garnier and Spier

The Action rejects claims 4, 30, 39-46, and 48 under 35 U.S.C. §103(a) as being unpatentable over Huyghe as applied to claims 1, 3, 8, 9-25, 29, 31, 32, 38, 47, 49, and 51-62, and further in view of Garnier *et al.* (C26) ("Garnier") and Spier *et al.* (C35) ("Spier"). It admits that Huyghe does not teach perfusion of the various culture systems recited, but argues that Garnier teaches scale-up adenovirus growth using medium replacement for controlling glucose concentration for improved virus yields in a bioreactor. The Action contends that the skilled artisan would have been motivated to use the system of Garnier with the method of Huyghe to produce larger quantities of adenovirus and that that person would have a reasonable expectation of success because both references concern using 293 cells to propagate adenovirus.

Moreover, it contends that Spier teaches the various culture systems claimed. Garnier is said to teach using a bioreactor. The Action concludes that the invention is *prima facie* obvious absent unexpected results. Applicants respectfully traverse this rejection.

As discussed above, the Examiner has failed to make a *prima facie* case that the 293 cells of Huyghe were infected at or after mid-log phase. Indeed, the evidence strongly supports the conclusion that the cells were, at best, in early log phase. Neither Garnier or Spier corrects this defect.

Moreover, Garnier concerns only the increased production of heterologous proteins using an adenovirus expression system and does not concern increased production of adenovirus. The Action is incorrect in asserting that Garnier teaches scale-up adenovirus growth for <u>improved virus yields</u>. The Garnier authors indicate, "[W]e present a two-step approach, undertaken to improve the volumetric yield of the [adenovirus] recombinant protein production system. . . ." Garnier at page 146. The data in the paper is focused on conditions that improve protein

production from the adenovirus, not improved levels of adenovirus production. In fact, the reference appears silent regarding when infection of the cells took place.

Because the goals of the present application and Garnier are very different, there would be no motivation to combine this reference with the Huyghe reference. In fact, the reference makes it clear that viral production is secondary to heterologous protein production as the authors describe how production of the heterologous protein is *greater* than the production of adenovirus structural proteins. As such, the reference teaches conditions to increase production of the heterologous protein at the expense of virus production The Federal Circuit held in *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Id.*; *see also* MPEP § 2143.01, page 2100-131. In this case, there is no such motivation.

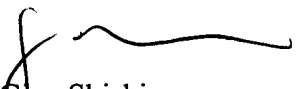
The Spier reference does not appear to even mention adenovirus. It does not suggest or motivate combining Huyghe and Garnier, much less suggest combining all three references. As such, a proper *prima facie* case of obviousness has not been made. Applicants respectfully request this rejection be withdrawn.

Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated June 3, 2004 . In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Listing of Pending claims:

30. A recombinant adenovirus composition comprising between 5 x 10^{14} and 1 x 10^{18} viral particles, prepared by a process comprising.

(a) preparing a culture of producer cells in a selected media;

(b) infecting producer cells in the culture with recombinant adenovirus, wherein the producer cells are infected between mid-log phase of growth and stationary phase of growth; and

(c) harvesting recombinant adenovirus from the cell culture.

31. The purified recombinant adenovirus composition of claim 30 or 41, said composition having one or more of the following properties:

(a) a virus titer of between about 1 x 10^{9} and about 1 x 10^{13} pfu/ml;

(b) a virus particle concentration between about 1 x 10^{10} and about 2 x 10^{13} particles/ml;

(c) a particle:pfu ratio between about 10 and about 60;

(d) having less than 50 ng BSA per 1 x 10^{12} viral particles;

(e) between about 50 pg and 1 ng of contaminating human DNA per 1 x 10^{12} viral particles,

(f) elutes essentially as a single elution peak upon HPLC.

32. The composition of claim 30 or 41, wherein the composition has a viral titer of between about 1 x 10^{11} and about 1 x 10^{13} pfu/ml.

33. The composition of claim 32, wherein the composition has a viral titer of between about 1×10^{12} and about 1×10^{13} pfu/ml.

34. The composition of claim 30 or 41, wherein the composition has a virus particle concentration between about 1×10^{11} and about 2×10^{13} particles/ml.

35. The composition of claim 34, wherein the composition has a virus particle concentration between about 1×10^{12} and about 1×10^{13} particles/ml.

36. The composition of claim 30 or 41, wherein the composition has a particle:pfu ratio between about 10 and about 50.

37. The composition of claim 36, wherein the composition has a particle:pfu ratio between about 10 and about 40.

38. The composition of claim 37, wherein the composition has a particle:pfu ratio between about 20 and about 40.

39. The composition of claim 30 or 41, wherein the composition has between about 1 ng and 50 ng BSA per 1×10^{12} viral particles.

40. The composition of claim 39, wherein the composition has between about 5 ng and 40 ng BSA per 1×10^{12} viral particles.

41. A purified recombinant adenovirus composition comprising between 5×10^{14} and 1×10^{18} adenoviral particles and between about 50 pg and 500 pg of contaminating human DNA per 1×10^{12} viral particles.

42. The composition of claim 30 or 41, wherein the composition has between about 100 pg and 500 pg of contaminating human DNA per 1×10^{12} viral particles.

43. The composition of claim 30 or 41, wherein the adenovirus of said composition elutes as essentially a single HPLC peak that comprises between 97 and 99% of the total area under the peak.

44. The composition of claim 30 or 41, wherein the composition has between about 50 pg and about 7 ng of contaminating human DNA per 1 x 10^{12} viral particles.

45. The composition of claim 44, wherein the composition has between about 50 pg and about 5 ng of contaminating human DNA per 1 x 10^{12} viral particles.

46. The composition of claim 45, wherein the composition has between about 50 pg and about 3 ng of contaminating human DNA per 1 x 10^{12} viral particles.

47. The composition of claim 46, wherein the composition has between about 50 pg and about 1 ng of contaminating human DNA per 1 x 10^{12} viral particles.